

AMENDMENT TO THE SPECIFICATION

Page 1, lines 7-11, please make the following amendments:

This is a continuation-in-part and claims priority to U.S. patent application Ser. No. 10/154,042 filed 21 May 2002 and U.S. patent application Ser. No. 10/623,057 filed 17 Jul. 2003; now U.S. Patent No. 7,105,308; priority is further claimed under U.S. provisional applications Ser. No. 60/459,888 filed 1 Apr. 2003; Ser. No. 60/494,482 filed 11 Aug. 2003; Ser. No. 60/508,034 filed 1 Oct. 2003; Ser. No. 60/512,941 filed 20 Oct. 2003; and Ser. No. 60/523,258 filed 18 Nov. 2003, all of the above of which are incorporated in their entirety by reference.

Page 6, lines 23-24, please make the following amendments:

FIGS. 10A-10C show data on the expression of heterodimers of IGF-1R and various Her receptors in frozen samples from human breast tissue. The amount of lysate assayed for two breast tumor samples that were positive for the indicated heterodimers is shown by (◆). FIG. 10A shows the expression of Her1-IGF-1R heterodimer (■). FIG. 10B shows the expression of Her2-IGF-1R heterodimer (■). FIG. 10C shows the expression of Her3-IGF-1R heterodimer (■).

Page 37, line 33 to page 38, line 25, please make the following amendments:

In one embodiment, a photosensitizer is incorporated into a latex particle to form photosensitizer beads, e.g. as disclosed by Pease et al., U.S. Pat. No. 5,709,994; Pollner, U.S. Pat. No. 6,346,384; and Pease et al, PCT publication WO 01/84157. Alternatively, photosensitizer beads may be prepared by covalently attaching a photosensitizer, such as rose bengal, to 0.5 micron latex beads by means of chloromethyl groups on the latex to provide an ester linking group, as described in J. Amer. Chem. Soc., 97: 3741 (1975). Use of such photosensitizer beads is illustrated in FIG. 3C. As described in FIG. 1C for heteroduplex

detection, complexes (330) are formed after combining reagents (1122) with a sample. This reaction may be carried out, for example, in a conventional 96-well or 384-well microtiter plate, or the like, having a filter membrane that forms one wall, e.g. the bottom, of the wells that allows reagents to be removed by the application of a vacuum. This allows the convenient exchange of buffers, if the buffer required for specific binding of binding compounds is different than the buffer required for either singlet oxygen generation or separation. For example, in the case of antibody-based binding compounds, a high salt buffer is required. If electrophoretic separation of the released tags is employed, then better performance is achieved by exchanging the buffer for one that has a lower salt concentration suitable for electrophoresis. In this embodiment, instead of attaching a photosensitizer directly to a binding compound, such as an antibody, a cleaving probe comprises two components: antibody ([332] 232) derivatized with a capture moiety, such as biotin (indicated in FIG. 3C as "bio") and photosensitizer bead (338) whose surface is derivatized with an agent ([334] 234) that specifically binds with the capture moiety, such as avidin or streptavidin. Complexes (330) are then captured (335) by photosensitizer beads by way of the capture moiety, such as biotin (336). Conveniently, if the pore diameter of the filter membrane is selected so that photosensitizer beads (338) cannot pass, then a buffer exchange also serves to remove unbound binding compounds, which leads to an improved signal. After an appropriate buffer for separation has been added, if necessary, photosensitizer beads (338) are illuminated so that singlet oxygen is generated (342) and molecular tags are released (344). Such released molecular tags (346) are then separated to form separation profile (352) and dimers are quantified ratiometrically from peaks (348) and (350). Photosensitizer beads may be used in either homogeneous or heterogeneous assay formats.

Please amend the Abstract as follows:

~~The invention is directed to a new class of biomarker in patient samples comprising heterodimers of Her cell surface membrane receptors. In one aspect, the invention includes a~~ A method of determining the status of a disease or healthful condition by correlating

such condition to amounts of one or more heterodimers of ErbB, or Her, cell surface membrane receptors measured directly in a patient sample ~~is described, in particular a fixed tissue sample.~~
~~In another aspect, the~~ The invention includes a method of determining a status of a cancer in a specimen from an individual by correlating measurements of amounts of one or more heterodimers of ErbB cell surface membrane receptors in cells of the specimen to such status, including presence or absence of a pre-cancerous state, presence or absence of a cancerous state, prognosis of a cancer, or responsiveness to treatment. Preferably, methods of the invention are implemented by using sets of binding compounds having releasable molecular tags that are specific for multiple components of one or more types of receptor dimers. After binding, molecular tags are released and separated from the assay mixture for analysis.